Statistical Segmentation of Biological Sequences

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2008 BIRC Workshop on Advances in Bioinformatics
16 February 2008

Acknowledgments

- Postdoctoral work in collaboration with:

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Cornell University

- Research funded by the US Department of Agriculture.

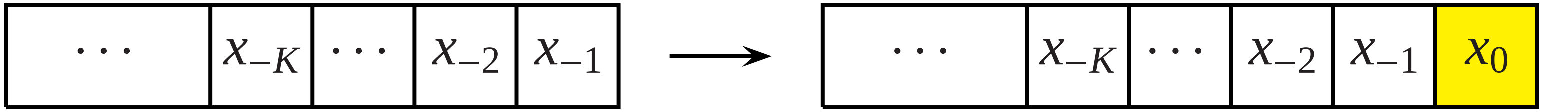
The Biological Sequence Segmentation Problem

- Two motivating problems:
  - HT segments (genomic islands) and lineage-specific segments (backbone) in bacterial DNA.
    - HT segments have different statistics from backbone.
    - Pathogenic genes frequently found near HT segment boundaries.
    - Gene-finding algorithms do not perform well in regions where statistics differ significantly from backbone.
    - Scoring problem even more severe for computational search of short regulatory elements.
  - Mesoscopic description of genome: 'Local' statistics vary along DNA sequence. Break long sequence into intermediate length segments, based on 'discernible' changes in statistics. Coarse-grained description.
- DNA polymerization along $5' \to 3'$ direction builds directionality into sequence. Biases in dinucleotide and codon frequencies. Model as Markov chains rather than Bernoulli chains with extended alphabets.

Markov chains

- State x_i of Markov chain at sequence position i can take on values in alphabet $\mathcal{S}$ of size S. Example. For DNA sequences, $\mathcal{S} = \{A, T, C, G\}$, and $S = 4$.

- Markov chains generated probabilistically. Existing subsequence extended



by attaching x_0 to end of subsequence with transition probability

$$p(x_0|x_{-1}x_{-2}\cdots x_{-K}).$$

- Markov chain of order K if $p(x_0|x_{-1}x_{-2}\cdots x_{-K'}) = p(x_0|x_{-1}x_{-2}\cdots x_{-K})$ for all $K' \geq K$.

- Transition probabilities can be organized into transition matrix

$$\mathbb{P} = [p_{\mathbf{t}s}], \quad s = 1, \ldots, S, \quad \mathbf{t} = t_1 \cdots t_K \in S^K.$$

- Equilibrium distribution $\boldsymbol{\pi} = (P_1, \ldots, P_k, \ldots, P_{S^K})$ such that $\boldsymbol{\pi}\mathbb{P} = \boldsymbol{\pi}$, P_k = probability of finding kth K-mer in stationary Markov chain.

Classification of Segmentation Schemes

- Matrix of segmentation schemes in literature:

	single−pass	recursive	local	global
sliding window average				
DNA walk				
dynamic programming				
hidden Markov model				

- All schemes rely on entropic measure of statistical dissimilarity, whether:
  - computed directly; or
  - in the form of inner product between quantized vectors of probabilities.

The Jensen-Shannon Divergence

- Given length-N sequence $\mathbf{x} = x_1 x_2 \cdots x_N$, $x_i = A, C, G, T$, assume composed of $M \geq 1$ Markov chains with boundaries at $i_1, \ldots, i_{M-1}$. M-segment sequence likelihood given by

$$P_M(\mathbf{x}; i_1, \ldots, i_{M-1}; \hat{\mathbb{P}}_1, \ldots, \hat{\mathbb{P}}_M) = \prod_{m=1}^{M} \prod_{\mathbf{t} \in S^K} \prod_{s=1}^{S} (\hat{p}^m_{\mathbf{t}s})^{f^m_{\mathbf{t}s}}; \qquad \hat{p}^m_{\mathbf{t}s} = \frac{f^m_{\mathbf{t}s}}{\sum_{s'} f^m_{\mathbf{t}s'}}.$$

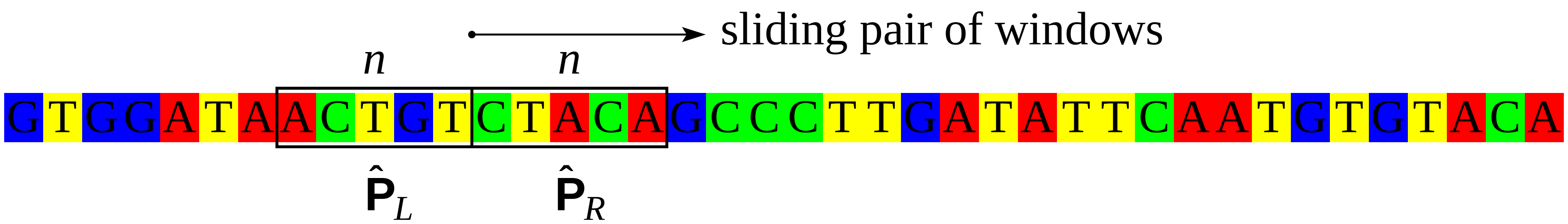
- Jensen-Shannon divergence

$$\Delta_M = \log \frac{P_M}{P_1} = -\sum_{\mathbf{t} \in S^K} \sum_{s=1}^{S} f_{\mathbf{t}s} \log \hat{p}_{\mathbf{t}s} + \sum_{m=1}^{M} \sum_{\mathbf{t} \in S^K} \sum_{s=1}^{S} f^m_{\mathbf{t}s} \log \hat{p}^m_{\mathbf{t}s};$$

$$f_{\mathbf{t}s} = \sum_{m=1}^{M} f^m_{\mathbf{t}s}, \qquad \hat{p}_{\mathbf{t}s} = \frac{f_{\mathbf{t}s}}{\sum_{s'=1}^{S} f_{\mathbf{t}s'}}$$

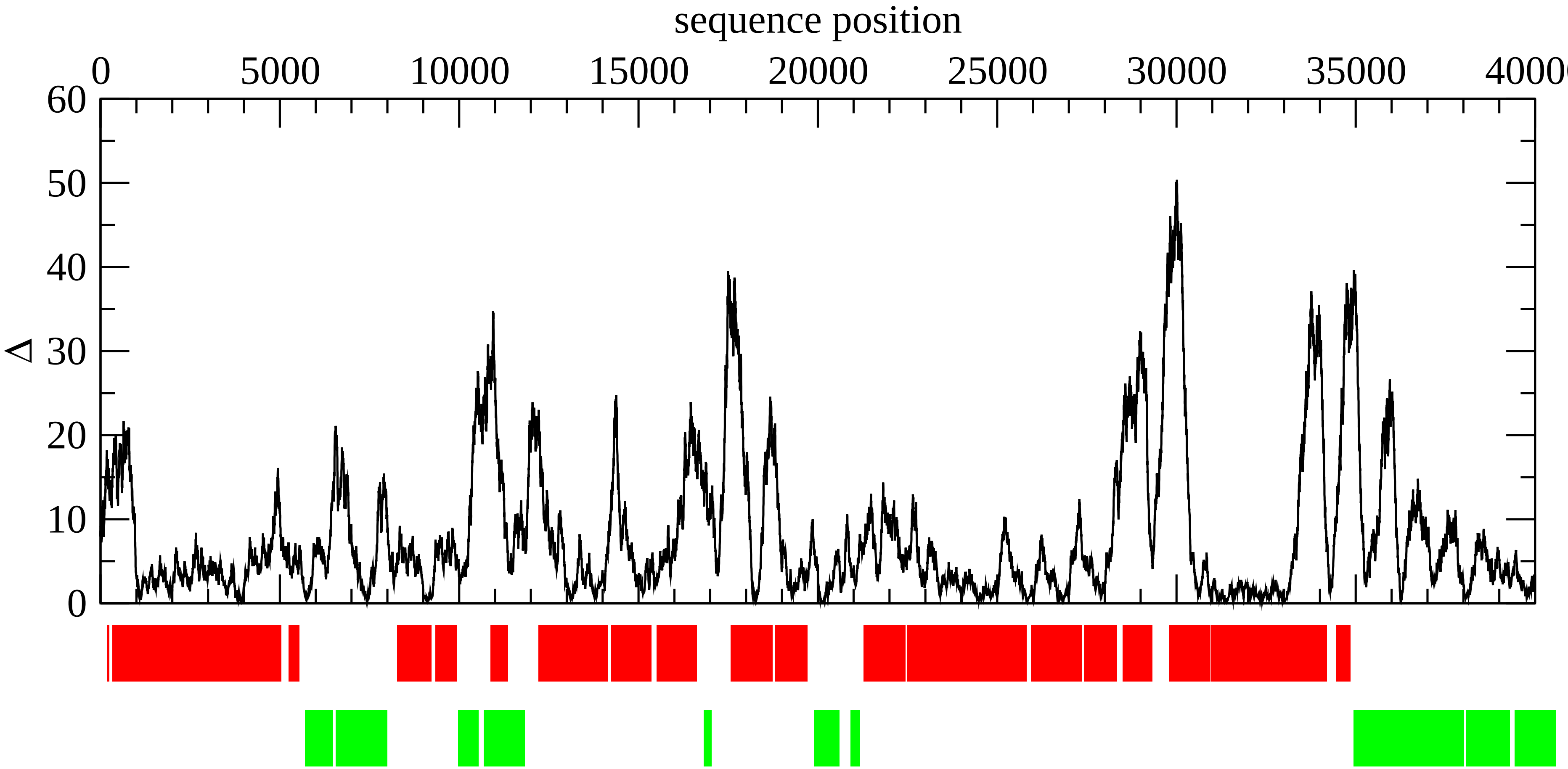
  is symmetric relative entropy providing quantitative measure of ‘goodness-of-fit’ of M-segment model over 1-segment model.

Segmentation with a Pair of Sliding Windows



- For a single sliding window of length n, spatial resolution decreases with n while statistical significance increases with n.
- Solution: To not compromise spatial resolution, use an adjoining pair of sliding windows, each of length n.
- Compute $\Delta_2(i)$ using $\hat{\mathbb{P}}_L$ in left window and $\hat{\mathbb{P}}_L$ in right window as function of sequence position i of centre of pair of windows.
- Segment boundaries appear as peaks in $\Delta_2(i)$. Strength of peak measure of statistical difference between the segments it separates.

Segmentation with a Pair of Sliding Windows

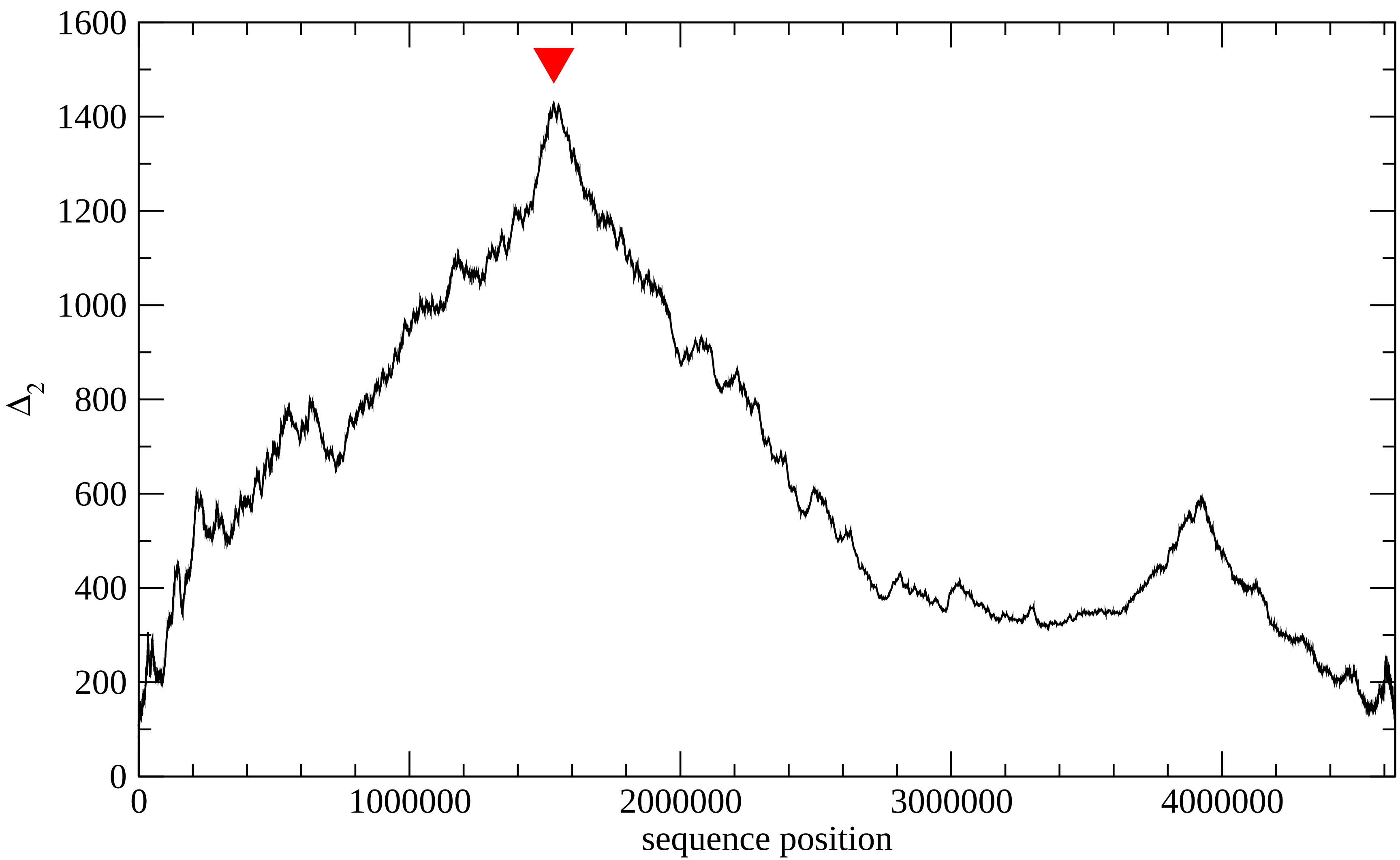


The interval $(0, 40000)$ in the *E. coli* K-12 MG1655 genome ($N = 4639675$), showing the $K = 0$ Jensen-Shannon divergence spectrum for $n = 1000$. Annotated genes on the positive (red) and negative (green) strands are shown below the graph.

Recursive Jensen-Shannon Segmentation

- STEP 1 (Segmentation):
  - Given sequence $\mathbf{x} = x_1 x_2 \cdots x_N$, compute 2-segment Jensen-Shannon divergence $\Delta_2(i)$ as function of cursor position i.
  - Find i^* such that $\Delta_2(i^*) = \max_i \Delta_2(i)$. The best 2-segment model for $\mathbf{x}$ is $\mathbf{x} = \mathbf{x}_L \mathbf{x}_R$, where $\mathbf{x}_L = x_1 \cdots x_{i^*}$ and $\mathbf{x}_R = x_{i^*+1} \cdots x_N$.
- STEP 2 (Recursion): Repeat STEP 1 for $\mathbf{x}_L$ and $\mathbf{x}_R$.
- STEP 3 (Termination): 1-segment model selected over 2-segment model if:
  - Hypothesis Testing: probability of obtaining divergence beyond observed Δ_2 greater than prescribed tolerance ϵ; or
  - Model Selection: information criterion (e.g. AIC, BIC) for 2-segment model greater than that for 1-segment model.

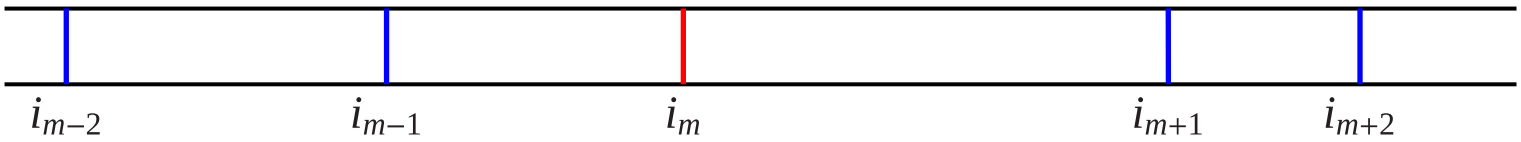
Recursive Jensen-Shannon Segmentation



Jensen-Shannon divergence spectrum of order $K = 3$ over the entire genome of *E. coli* K-12 MG1655 ($N = 4639675$ bp). The first segment boundary to be obtained in this first stage of recursive segmentation is shown by the red arrow.

Segmentation Optimization

- Two procedures to optimize segment boundary i_m if we are allowed to move only one segment boundary at a time:



  - First-order update: Compute $\Delta_2^m(i)$ for supersegment (i_{m-1}, i, i_{m+1}), and choose $i_m = i^*$, such that $\Delta_2(i^*) = \max_{i_{m-1}<i<i_{m+1}} \Delta_2(i)$, to be new position of segment boundary.
  - Second-order update: Compute $\Delta_2^{m-1}(i)$ for supersegment (i_{m-2}, i_{m-1}, i) and $\Delta_2^{m+1}(i)$ for supersegment (i, i_{m+1}, i_{m+2}), and choose $i_m = i^*$, such that

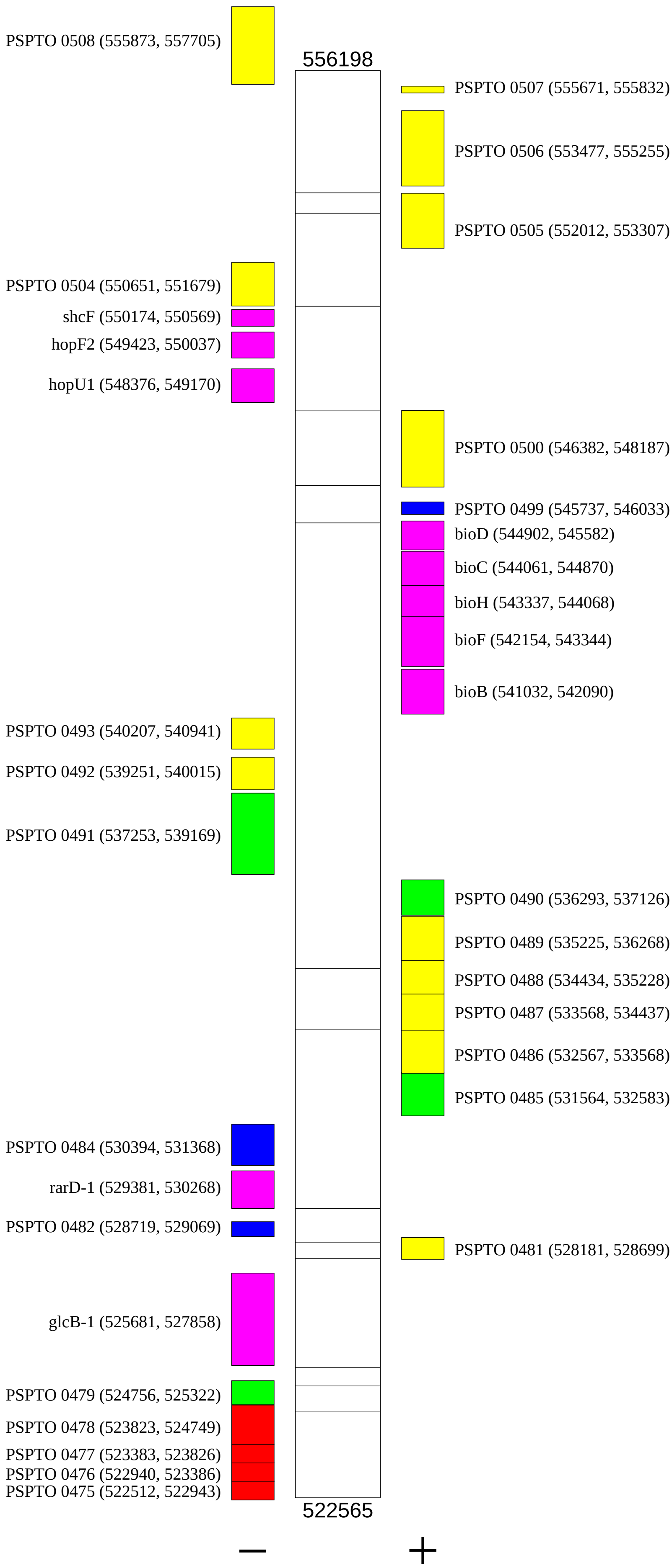
$$\Delta_2^{m-1}(i^*) + \Delta_2^{m+1}(i^*) = \max_{i_{m-1}<i<i_{m+1}} \left[\Delta_2^{m-1}(i) + \Delta_2^{m+1}(i)\right],$$

    to be new position of segment boundary.

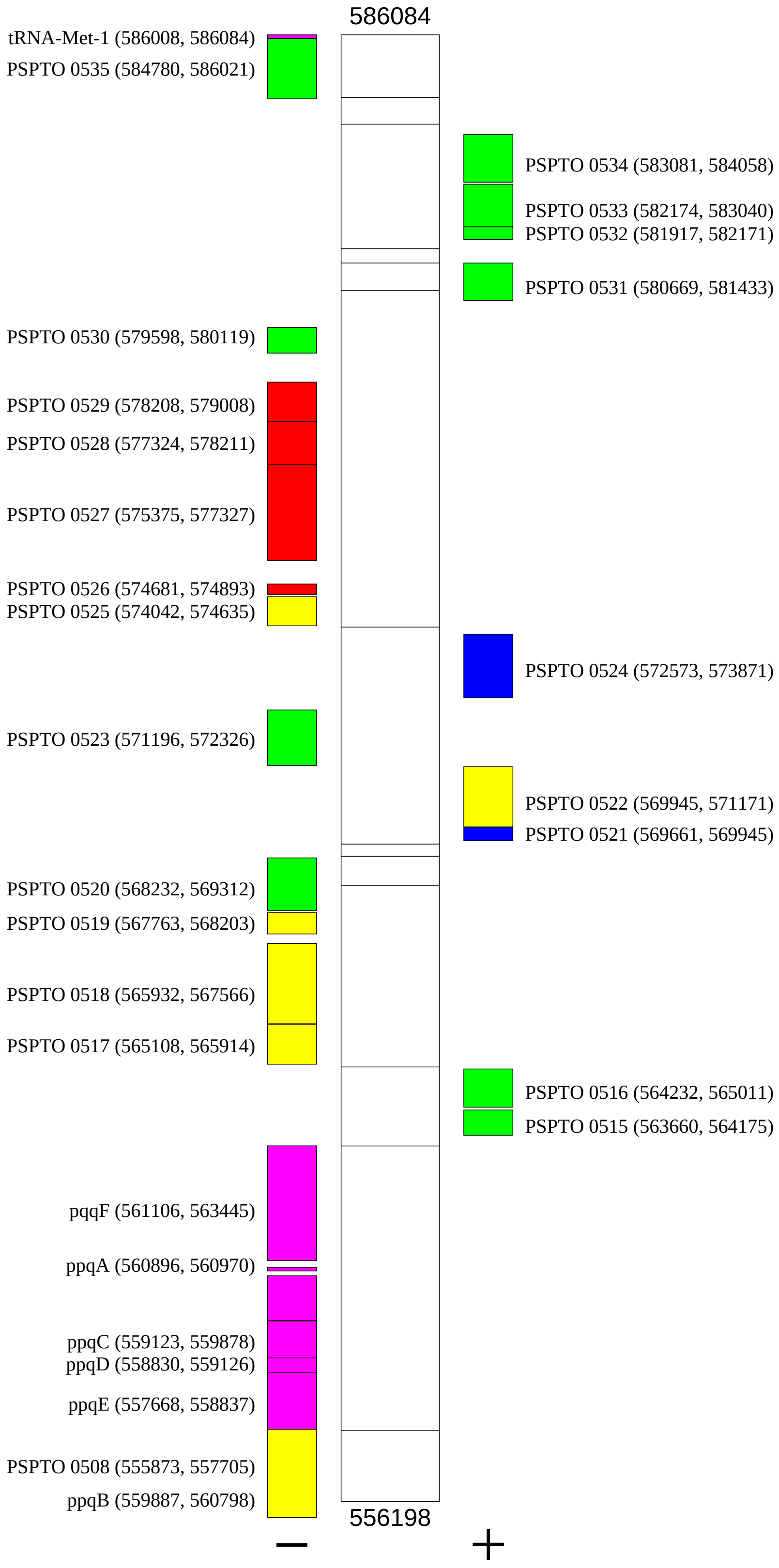
- Segment boundaries $\{i_m\}_{m=1}^M$ updated serially, or in parallel.

- Optimized recursive segmentation: Right after STEP 1 (Segmentation), optimize segmentation using first- or second-order update algorithm.

Optimized Recursive Jensen-Shannon Segmentation



Optimized Recursive Jensen-Shannon Segmentation



Conclusions & Further Works

- In conclusion, we have:
  - Developed segmentation scheme using a pair of sliding windows;
  - Developed optimization algorithms for recursive Jensen-Shannon segmentation scheme; and
- Further works:
  - Mean-field analysis of sliding window segmentation scheme: mean-field lineshape and match filtering;
  - Mean-field analysis of recursive segmentation scheme: identified problem of context sensitivity;
  - Developed new termination criterion based on intrinsic statistical fluctuations.
  - Incomplete segmentation misleading, cluster terminal segments instead to obtain coarser scale description of genome. E.g. to distinguish lineage-specific regions arising from HGT and the genetic backbone.
  - Multiple sequence clustering for comparative, phylogenetic studies.